Interference

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Dean Engelhardt et al	
Serial No.:	08/486,069	Group Art Unit: 1631
Filed:	June 7, 1995	Ex'r: Ardin H. Marschel, Ph.D.

For: **NUCLEIC ACID SEQUENCING PROCESSES USING NON-RADIOACTIVE DETECTABLE MODIFIED OR LABELED NUCLEOTIDES OR NUCLEOTIDE ANALOGS, AND OTHER PROCESSES FOR NUCLEIC ACID DETECTION AND CHROMOSOMAL CHARACTERIZATION USING SUCH NON-RADIOACTIVE DETECTABLE MODIFIED OR LABELED NUCLEOTIDES OR NUCLEOTIDE ANALOGS**

September 28, 2004

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

REQUEST FOR INTERFERENCE PURSUANT TO 37 C.F.R. §41.202

Applicants filed a first Request for Interference between U.S. Patent Application No. 08/486,069 (the "Engelhardt Application" or the "'069 Application") and U.S. Patent Number 5,821,058 (the "Smith Patent" or the "'058 Patent") on December 21, 2001. The Request was denied in the Office Action of July 1, 2003. Applicants respectfully request reconsideration in view of this Request, the Amendments filed December 31, 2003 and September 14, 2004, and the Amendment filed herewith, which are responsive to the grounds for denial set forth in the July 1 Office Action. This Request reflects all claim amendments, additions and cancellations since the first Request was filed. This Request also includes additional explanation about why the application claims and the patent claims correspond to the new counts.

Below is the information required by 37 C.F.R. § 41.202(a) under headings that correspond to the six subsections of § 41.202(a).

REQUIREMENTS OF 37 C.F.R. § 41.202(a)(1-6)

1. Identification of the Patent

Applicants request an interference against U.S. Patent No. 5,821,058, issued October 13, 1998, to Lloyd M. Smith, Leroy E. Hood, Michael W. Hunkapiller, Tim J. Hunkapiller and Charles R. Connell (collectively "Smith"). The patent purports on its face to be assigned to the California Institute of Technology, Pasadena, California.

2. Identification of Interfering Claims; Presentation of Proposed Counts; Showing of Correspondence Between Interfering Claims and Proposed Counts

A. Presentation of Proposed Counts

Applicants attach hereto Appendix A which includes proposed Counts 1 and 2. For the Examiner's convenience, Counts 1 and 2 are reproduced below.

Proposed Count 1:

A method of separating and detecting tagged polynucleotides which comprises:

providing a plurality of polynucleotides, each tagged with a chromophore or fluorophore;

resolving to separate one of the plurality of tagged polynucleotides from the other tagged polynucleotides differing in length by a single nucleotide using an electrophoretic procedure capable of resolving tagged polynucleotides differing by a single nucleotide; and

detecting the resolved tagged polynucleotides by means of the chromophore or fluorophore;

or

A process for resolving or separating non-radioactively labeled nucleic acid fragments with a sequencing gel, comprising:

providing or generating detectable non-radioactively labeled nucleic acid fragments comprising one or more nucleotides that may be attached to, or coupled to, or incorporated into DNA or RNA, and wherein one or more fluorescent indicators are covalently attached, directly or through a linkage group, to the furanosyl moiety, the phosphate moiety, the base moiety of said nucleotides, or any combination thereof;

subjecting said labeled fragments to a sequencing gel to separate or resolve said fragments; and

detecting non-radioactively said separated or resolved fragments by means of said fluorescent indicators attached to said nucleotides.

Proposed Count 2:

A method for determining the sequence of a polynucleotide which comprises:

providing polynucleotide fragments generated by a polynucleotide sequencing technique, which are tagged with chromophores or fluorophores, wherein the fragments from one or more of the four sequencing reactions A, C, G or T are distinguishable from fragments of the other reactions by their spectral characteristics;

resolving the fragments by electrophoresis;

detecting the fragments as they are being resolved by means of the spectral characteristics of the chromophores or fluorophores, and thereby determining the polynucleotide sequence based on the polynucleotide fragments detected;

or

A process for determining the sequence of a nucleic acid of interest comprising:

providing at least one nucleic acid of interest;

generating detectable non-radioactively labeled nucleic acid fragments complementary to said nucleic acid of interest or a portion thereof, wherein said fragments have been labeled by incorporation of one or more nucleoside triphosphates comprising different fluorescent indicators;

subjecting said labeled fragments to a sequencing gel to separate or resolve said fragments; and

detecting said separated or resolved fragments by means of said different fluorescent indicators, to determine the sequence of said nucleic acid of interest.

B. Identification of All Interfering Claims

In accordance with § 41.202(a)(2), Applicants respectfully submit that the following claims interfere:

Engelhardt Claims 638, 642, 660, 661, 670, 707, 711, 712, 714, 790, 794, 812, 813, 822, 859, 863, 864, 866, 871, 942, 946, 964, 965, 974, 1011, 1015, 1016, 1018, 1023, 1094, 1098, 1116, 1117, 1126, 1163, 1167, 1168, 1170, 1175, 1249, 1267-1270, 1272, 1278, 1288, 1289, 1291, 1297, 1739, 1767, 1768, 1782, 1783 and 1795 interfere with Smith Claims 1-7, 9-16, 19, 23-27 and 54-56; and

Engelhardt Claims 1769-1773, 1775 and 1796 interfere with Smith Claims 8, 17, 18, 20-22 and 28-53.

C. Showing of Correspondence Between the Interfering Claims and the Proposed Counts

The inventions defined by the proposed counts are only two of several different inventions disclosed in the Engelhardt Application. However, they are appropriately used to define the subject matter of the interference because they constitute separate patentable inventions from the other inventions disclosed.

(1) Smith Claims Corresponding to Proposed Count 1.

Smith Claims 1-7, 9-16, 19, 23-27 and 54-56 correspond to Count 1. 37 C.F.R. § 41.207(b)(2) states that a claim "corresponds" to a count "if the subject matter of the count, treated as prior art to the claim, would have anticipated or rendered obvious the subject matter of the claim."

Applicants first address the correspondence of the independent claims to Count 1. Smith Claim 1 corresponds exactly to Count 1, and is thus necessarily anticipated by the count.

Smith Claim 7 corresponds to Count 1 because it recites the same basic steps as Count 1, and further recites that each of the tagged polynucleotides is "an identical primer oligonucleotide." Such identical primer oligonucleotides were well known and widely used in the prior art for the primer extension reactions in Sanger-type sequencing.[1] Therefore, the invention of Claim 7 is obvious in view of the invention of Count 1.

Smith Claim 14 recites the same basic steps as Count 1 and further recites: "and determining the polynucleotide sequence from the polynucleotide fragments detected." Claim 14 is not patentably distinct from Count 1. Count 1 is directed to a method of separating and detecting polynucleotides which differ from each other by a single nucleotide in length using chromophores or fluorophores. It was and remains long accepted practice that the primary reason for separating and detecting polynucleotides that differ from each other by a single nucleotide in length is to determine the sequence of the polynucleotide or variation therein. Indeed, there was little if any practical utility for single nucleotide resolution outside of sequencing at the time of the invention. Since separating and detecting

[1] *See, e.g.*, Smith, column 1, lines 59 to column 2, line 1; column 4, lines 28-41; Claims 8, 10 and 25.

are part and parcel of sequencing, the recitation of "determining the polynucleotide sequence" in Claim 14 is obvious in view of Count 1 and what was known in the art.[2]

Smith Claim 54 recites the same basic steps as Count 1 and further recites the step of "analyzing the sizes of the separated tagged fragments" to determine the sequence of the "single-stranded" polynucleotide. For the same reasons discussed above with respect to Claim 14, Claim 54 is not patentably distinct from Count 1. Analyzing the sizes of the separated tagged fragments to determine the polynucleotide sequence is obvious in view of Count 1, which teaches separating and detecting polynucleotide fragments which differ from each other by a single nucleotide in length.

Applicants now address the correspondence of the dependent claims to Count 1. Smith Claims 2-6, 9-13, 15-27 and 55-56 correspond to Count 1 because they define substantially the same patentable invention as Count 1. Claims 2 and 15 recite that the polynucleotide is DNA. Because the polynucleotide of Count 1 would normally be DNA, the dependent claims' recitation that the polynucleotide is DNA does not patentably distinguish the claims from Count 1 as "DNA" is an obvious variant of "polynucleotide."

Smith Claims 3 and 19 recite that the polynucleotide is obtained by chemical degradation. The term "chemical degradation" in these claims is shorthand for the Maxam-Gilbert reaction, which is well known and widely used in the prior art.[3] As such, these claims add nothing to patentably distinguish them from Count 1.

Smith Claims 4 and 24 recite that the detecting occurs during the electrophoresis. Count 1 recites "using an electrophoretic procedure." Furthermore, the Smith specification indicates that Count 1 (Smith Claim 1) encompasses "the detection and characterization of

---

[2] The Smith specification, file history and claims are and always have been directed to either sequence determination or the separating and detecting components of sequence determination. Indeed, the title of the invention is an "Automated DNA *Sequencing* Technique." (emphasis added). At column 3, lines 8-17, Smith states, "Briefly, this invention comprises a novel process for the eletrophoetic [sic] analysis of DNA fragments produced in DNA, sequencing operations wherein chromophores or fluorophores are used to tag the DNA fragments produced by the sequencing chemistry and permit the detection and characterization of the fragments as they are resolved by electrophoresis through a gel."

[3] *See* Smith, column 2, lines 18-38; column 5, lines 44-46; Claim 25.

the fragments as they are resolved by electrophoresis through a gel."[4] Accordingly, Count 1 anticipates or renders obvious Claims 4 and 24.

Smith Claims 5, 6, 12, 13, 26, 27, 55 and 56 recite that the fluorescent or chromophoric tags are detected with a laser or high-intensity monochromatic light source. Use of lasers and high-intensity monochromatic light to detect fluorescent or chromophoric tags was well known and widely used in the prior art.[5] Therefore, these claims are obvious in view of Count 1 and the prior art.

Smith Claims 9 and 23 recite that, prior to electrophoresis, the tags are coupled to the polynucleotide fragments via amine linkages. Count 1 does not specify the means by which the tags are coupled to the polynucleotide fragments and thus Count 1 encompasses all means of coupling. Coupling tags to polynucleotide fragments via amine linkages is thus a species of Count 1. Although a genus does not always anticipate a species, the genus of Count 1 anticipates the species of Claims 9 and 23 because in the Smith Patent these species are the main examples of the genus.[6] At the least, Count 1 renders these species obvious in view of the prior art.[7]

Smith Claims 10 and 11 require that the primer be tagged in a way that does not interfere with extension by a polymerase. Because this was a well-known requirement of prior art sequencing, it does not render Claims 10 and 11 patentably distinct from Count 1.

---

[4] *See, e.g.*, Smith, column 3, lines 12-17.

[5] *See, e.g.*, Cotrufo et al., "High sensitivity method for fluorofore detection in gradient polyacrylamide slab gels through excitation by laser light: Application to glycoproteins stained with concanavalin A-fluorescein isothiocyanate," *Anal. Biochem.* (1983) 134:313-319.

[6] *See, e.g.*, Smith, Example III at column 7, line 60 to column 8, line 2.

[7] With regard to tagging amino-derivatized oligonucleotides and preparing phosphoramidites for use in detecting polynucleotides, the following five patents appear to qualify as prior art to the Smith Patent under 35 U.S.C. §102(e): U.S. 4,849,513, U.S. 4,849,513, U.S. 5,015,733, U.S. 5,118,800 and U.S. 5,118,02. These patents name Smith as an inventor, but the other named inventors differ from the inventors named on the Smith Patent at issue in this interference. *See also* the parent application of these five patents, U.S. Pat. App. No. 565,010, filed December 20, 1983. (After filing the '010 application, relevant disclosure related to tagging chemistry was cancelled from it by amendment. Before the disclosure was cancelled, however, the '010 application was incorporated by reference into the Smith Patent at issue in this interference. *See* Smith, column 5, lines 4-8.)

Smith Claim 16 refers to an identical primer oligonucleotide. As discussed above with respect to Claim 7, identical primer oligonucleotides were well known and widely used in the prior art for the primer extension reactions in Sanger-type sequencing. Accordingly, the invention of Claim 17 is obvious view of Count 1.

Smith Claim 25 recites that the technique used to determine the sequence in Claim 14 is either the Sanger or the Maxam-Gilbert technique. Both of these techniques were well known in the art and their recitation in Claim 25 does not render Claim 25 patentably distinct from Count 1.

(2) Engelhardt Claims Corresponding to Proposed Count 1.

The following Engelhardt claims correspond to proposed Count 1: 638, 642, 660, 661, 670, 707, 711, 712, 714, 790, 794, 812, 813, 822, 859, 863, 864, 866, 871, 942, 946, 964, 965, 974, 1011, 1015, 1016, 1018, 1023, 1094, 1098, 1116, 1117, 1126, 1163, 1167, 1168, 1170, 1175, 1249, 1267-1270, 1272, 1278, 1288, 1289, 1291, 1297, 1739, 1767, 1768, 1782, 1783 and 1795.

Engelhardt Claim 1768 corresponds exactly to Count 1, and is thus necessarily anticipated by the count.

Engelhardt Claims 638, 642, 660, 661, 670, 707, 711, 712, 714, 790, 794, 812, 813, 822, 859, 863, 864, 866, 871 942, 946, 964, 965, 974, 1011, 1015, 1016, 1018, 1023, 1094, 1098, 1116, 1117, 1126, 1163, 1167, 1168, 1170, 1175 and 1739 correspond to Count 1. These claims include the step of "determining the sequence" of polynucleotides resolved and detected on a sequencing gel.[8] Count 1 recites the step of resolving or separating labeled

[8] Claims 638, 642, 660, 661, 670, 707, 711, 712 and 714 depend from Claim 569. Claims 790, 794, 812, 813, 822, 859, 863, 864, 866 and 871 depend from Claim 721. Claims 942, 946, 964, 965, 974, 1011, 1015, 1016, 1018 and 1023 depend from Claim 873. Claims 1094, 1098, 1116, 1117, 1126, 1163, 1167, 1168, 1170 and 1175 depend from Claim 1025. Each of the independent Claims 569, 721, 873 and 1075 recites a process for "determining the sequence" of a labeled nucleic acid of interest comprising separating or resolving the nucleic acids on a sequencing gel and detecting the nucleic acids by means of the non-radioactive label. Since dependent claims necessarily include all the limitations of the independent claims from which they depend, Claims 638, 642, 660, 661, 670, 707, 711, 712, 714, 790, 794, 812, 813, 822, 859, 863, 864, 866, 871 942, 946, 964, 965, 974, 1011, 1015, 1016, 1018, 1023, 1094, 1098, 1116, 1117, 1126, 1163, 1167, 1168, 1170, 1175 and 1739 necessarily include the step of "determining the sequence" of a polynucleotide resolved and detected on a sequencing gel.

nucleic acid fragments "with a sequencing gel." One skilled in the art at the time of the invention would recognize that the only practical purpose for resolving and detecting polynucleotides "with a sequencing gel" would have been to determine the sequence of the polynucleotide so resolved and detected. As such, the recitation of "determining the polynucleotide sequence" in Engelhardt Claims 638, 642, 660, 661, 670, 707, 711, 712, 714, 790, 794, 812, 813, 822, 859, 863, 864, 866, 871 942, 946, 964, 965, 974, 1011, 1015, 1016, 1018, 1023, 1094, 1098, 1116, 1117, 1126, 1163, 1167, 1168, 1170, 1175 and 1739 does not patentably distinguish the claims from Count 1. Furthermore, each of these dependent claims recite that the indicator (or tag) can be, among other things, a fluorescent molecule. Since Count 1 recites that the tag is a "fluorescent indicator," the count anticipates or renders obvious each of the claims.

Engelhardt Claims 1249, 1267-1270, 1272, 1278, 1288, 1289, 1291, and 1297 correspond to Count 1. These claims include the step of "incorporating one or more labeled nucleotides into the polynucleotides."[9] Count 1 recites, "providing or generating detectable non-radioactively labeled nucleic acid fragments comprising one or more nucleotides that may be attached to, or coupled to, or incorporated into DNA or RNA" before the polynucleotides are resolved and detected. Inherent in Count 1's recitation of providing or generating labeled polynucleotides is the step of incorporating one or more labeled nucleotides into the polynucleotides. Indeed, since polynucleotides are not naturally labeled, one cannot "provide" or "generate" a labeled polynucleotide without first labeling it, i.e., incorporating a labeled nucleotide into the polynucleotide. Accordingly, the recitation of incorporating one or more labeled nucleotides into one or more nucleic acids of interest in

[9] Claims 1249, 1267-1270, 1272, 1278, 1288, 1289, 1291, and 1297 all depend from Claim 1177, which is a process for determining with a sequencing gel the presence of non-radioactively labeled nucleic acids complementary to a nucleic acid of interest comprising separating or resolving nucleic acids on a sequencing gel and detecting the presence of the nucleic acid fragments by means of the non-radioactive label. Claim 1177 further recites the step of incorporating one or more labeled nucleotides into one or more nucleic acids of interest before transferring the resulting labeled nucleic acid(s) of interest to a sequencing gel to be resolved and detected. Since dependent claims necessarily include all the limitations of the independent claims from which they depend, Claims 1249, 1267-1270, 1272, 1278, 1288, 1289, 1291, and 1297 necessarily include the step of "incorporating one or more labeled nucleotides into the polynucleotides."

Claim 1177, from which Claims 1249, 1267-1270, 1272, 1278, 1288, 1289, 1291, and 1297 all depend, does not patentably distinguish the claims from Count 1. Furthermore, each of these dependent claims recite that the indicator (or tag) can be, among other things, a fluorescent molecule. Since Count 1 recites that the tag is a "fluorescent indicator," the count anticipates or renders obvious each of the claims.

Engelhardt Claims 1767, 1782 and 1783 correspond to Count 1. Claims 1767 and 1782 are directed to a process for detecting nucleic acid fragments labeled with one or more fluorescent indicators comprising subjecting the fragments to a sequencing gel to separate or resolve the fragments and detecting the fragments by means of the fluorescent indicator. Claim 1783 is a process for resolving or separating nucleic acid fragments labeled with one or more fluorescent indicators comprising subjecting the fragments to a sequencing gel to separate or resolve the fragments and detecting the fragments by means of the fluorescent indicator. Count 1 recites the same basic steps as Claims 1767, 1782 and 1783 and thus anticipates or renders obvious these claims.

Engelhardt Claim 1795 corresponds to Count 1. Claim 1795 is a process for determining the sequence of a nucleic acid of interest comprising providing or generating nucleic acid fragments labeled with one or more fluorescent indicators, subjecting the fragments to a sequencing gel to separate or resolve the fragments, detecting the fragments by means of the fluorescent indicator, and determining the sequence of the nucleic acid of interest from the detected fragments. As discussed above, one skilled in the art at the time of the invention would recognize that the only practical purpose for resolving and detecting polynucleotides "with a sequencing gel" (as recited in Count 1) would have been to determine the sequence of the polynucleotide so resolved and detected (as recited in Claim 1795). As such, the recitation of "determining the polynucleotide sequence" in Engelhardt Claim 1795 does not patentably distinguish the claim from Count 1.

(3) Smith Claims Corresponding to Proposed Count 2.

Smith Claims 8, 17, 18, 20-22 and 28-53 correspond to Count 2.

Smith Claim 41 corresponds exactly to Count 2, and is thus necessarily anticipated by the count.

Smith Claim 28 recites a method for determining the sequence of a polynucleotide comprising providing "fragments tagged with chromophores or fluorophores are distinguishable from others by their spectral characteristics." Count 2 states that such fragments must be "from one or more of the four sequencing reactions A, C, G or T." The fragments from one or more of the four sequencing reactions A, C, G or T of Count 2 necessarily include the "fragments tagged with chromophores or fluorophores" of Claim 28. Accordingly, Count 2 anticipates or renders obvious Claim 28.

Smith Claims 18, 37 and 51 recite that, after the sequencing reaction, the tags are coupled to the polynucleotide fragments via a deblocked amino group. Dependent Claim 36 recites that, prior to electrophoresis, the tags are coupled to the polynucleotide fragments via amine linkages. The genus of Count 2 anticipates or renders obvious the species of Claims 18, 36, 37 and 51 because in the Smith Patent these species are the main examples of the genus.

Smith Claims 29 and 42 recite that the polynucleotide is DNA. Because the polynucleotide of Count 2 would normally be DNA, the dependent claims' recitation that the polynucleotide is DNA does not patentably distinguish the claims from Count 2 as "DNA" is an obvious variant of "polynucleotide".

Smith Claims 30 and 43 recite that each of the tagged polynucleotides is "an identical primer oligonucleotide sequence." Such identical primer oligonucleotides were well known and widely used in the prior art for the primer extension reactions in Sanger-type sequencing.[10] Accordingly, Claims 30 and 43 are obvious in view of Count 2 and the prior art.

Smith Claims 31 and 44 recite that the method entails chemical degradation. In these claims, the term "chemical degradation" is shorthand for the Maxam-Gilbert reaction well known in the prior art.[11] As such, Claims 31 and 44 add nothing to patentably distinguish them from Count 2.

Smith Claims 35 and 48 state that the fluorophore is one of three specific fluorophores: "fluorescein, tetramethyl rhodamine, or substituted rhodamine." These three

---

[10] *See, e.g.*, Smith, column 1, lines 59 to column 2, line 1; column 4, lines 28-41; Claims 8, 10 and 25.

[11] *See* Smith, column 2, lines 18-38; column 5, lines 44-46; Claim 25.

fluorophores, which were commercially available when the Smith application was filed, were well known in the prior art and add nothing to patentably distinguish Claims 35 and 48 from Count 2.[12]

Smith Claims 39, 40, 52 and 53 recite that the fluorescent or chromophoric tags are detected with a laser or high-intensity monochromatic light source. Use of lasers and high-intensity monochromatic light to detect such tags was well known and obvious in view of the prior art.[13]

The remaining dependent claims, Claims 8, 17, 20-22, 29-40 and 42-53 correspond to Count 2 because they define substantially the same patentable invention as Count 2. Count 2 states that the "fragments from one or more of the four sequencing reactions A, C, G or T are distinguishable from fragments of the other reactions by their spectral characteristics." Claims 8, 17, 20-22, 28, 32-34, 38, 45-47, 49 and 50 recite minor variations of this feature. Count 2 would anticipate or render obvious these variations in view of the art.

(4) Engelhardt Claims Corresponding to Proposed Count 2.

Engelhardt Claims 1769-1773, 1775 and 1796 correspond to proposed Count 2.

Engelhardt Claim 1769 corresponds exactly to Count 2, and is thus necessarily anticipated by the count.

Engelhardt Claims 1770-1773 and 1775 correspond to Count 2. These claims depend from Claim 1769 (Count 2), which recites a process for determining the sequence of a nucleic acid of interest comprising generating labeled nucleic acid fragments complementary to said nucleic acid of interest, wherein said fragments have been labeled by incorporation of one or more nucleoside triphosphates comprising different fluorescent indicators, subjecting the fragments to a sequencing gel to separate or resolve the fragments, and detecting the fragments by means of the different fluorescent indicators to determine the sequence of the nucleic acid of interest. Claim 1770 further recites that that the

---

[12] *See infra*, five patents and application in footnote 7. *See also* Smith, column 7, lines 46-52.

[13] *See, e.g.*, Cotrufo et al., "High sensitivity method for fluorofore detection in gradient polyacrylamide slab gels through excitation by laser light: Application to glycoproteins stained with concanavalin A-fluorescein isothiocyanate," *Anal. Biochem.* (1983) 134:313-319.

nucleoside triphosphate comprising the fluorescent indicator comprises a furanosyl moiety. The labeled nucleic acid fragments of Count 2 are composed of ribonucleotides and/or deoxyribonucleotides, which necessarily comprise a furanosyl moiety. Accordingly, Count 2 anticipates or renders obvious Claim 1770.

Claim 1771 depends from Claim 1770 and further recites that the furanosyl moiety comprises a ribose, 2'-deoxyribose, 3'-deoxyribose or 2',3'-dideoxyribose. The labeled nucleic acid fragments of Count 2 are composed of ribonucleotides and/or deoxyribonucleotides, which necessarily comprise one or more ribose, 2'-deoxyribose, 3'-deoxyribose or 2',3'-dideoxyribose. Accordingly, Count 2 anticipates or renders obvious Claim 1771.

Claim 1772 depends from Claim 1769 and further recites that the nucleoside triphosphate comprises fluorescein, rhodamine or dansyl. The nucleic acid fragments of Count 2 are labeled with a "fluorescent indicator." Since fluorescein, rhodamine or dansyl were well known in the art at the time of the invention, they would have been obvious in view of the count. Accordingly, Count 2 anticipates or renders obvious Claim 1772.

Claim 1773 depends from Claim 1769 and further recites that the one or more nucleoside triphosphates comprise a base moiety or a base analog comprising a purine, a purine analog, a 7-deazapurine, a 7-deazapurine analog, a pyrimidine, or a pyrimidine analog. The labeled nucleic acid fragments of Count 2 are composed of nucleoside triphosphates which necessarily comprise a phosphate, sugar and base moiety. The base moiety normally comprises a purine, 7-deazapurine, pyrimidine, and/or an analog thereof. Accordingly, Count 2 anticipates or renders obvious Claim 1773.

Claim 1775 depends from Claim 1773 and further recites that the fluorescent indicators are attached to said purine, 7-deazapurine, pyrimidine, or analogs thereof. Count 2 recites that the fragments have been labeled by different fluorescent indicators, but does not indicate what component of the nucleotide comprises the fluorescent indicators. However, since there are only three components of a nucleotide to which a label could be attached (e.g., the base, phosphate or sugar), it would have been obvious to attach the fluorescent indicator to the base of the nucleotide (e.g., a purine, 7-deazapurine, pyrimidine, or analogs thereof) in view of Count 2. Accordingly, Count 2 anticipates or renders obvious Claim 1775.

Engelhardt Claim 1796 corresponds to Count 2. Claim 1796 is a process for determining the sequence of a nucleic acid of interest comprising providing or generating nucleic acid fragments labeled with one or more different fluorescent indicators, subjecting the fragments to a sequencing gel to separate or resolve the fragments, detecting the fragments by means of the fluorescent indicator, and determining the sequence of the nucleic acid of interest from the detected fragments. Count 2 recites the same basic steps as Claim 1796 and thus anticipates or renders obvious the claim.

3. Claim Charts Comparing Each Party's Correspondence to the Counts and Showing of Why the Claims Interfere

In accordance with 37 C.F.R. § 41.202(a)(3), attached Appendix B sets forth a side-by-side comparison of Count 1, Smith Independent Claims 1 and 14, Engelhardt Independent Claims 1768 and 1795, and a showing of why the Smith and Engelhardt claims interfere within the meaning of 37 C.F.R. § 41.203(a).[14]

Similarly, attached Appendix C sets forth a side-by-side comparison of Count 2, Smith Independent Claim 41 and 28, Engelhardt Independent Claims 1769 and 1796, and a showing of why the Smith and Engelhardt claims interfere within the meaning of section 41.203(a).

4. Explanation of Why Applicants Will Prevail On Priority

The Engelhardt Application is a continuation of Serial No. 07/954,772, filed on September 30, 1992, now abandoned, which is a continuation of Serial No. 07/548,348, filed on July 2, 1990, now abandoned, which is a division of Serial No. 07/140,980, filed on January 5, 1988, now abandoned, which is a continuation of Serial No. 06/391,440, filed on June 23, 1982, now abandoned. As each of these applications is a continuation, the effective priority date for each of the Engelhardt claims is June 23, 1982.

---

[14] 37 C.F.R. § 41.203(a) provides:

(a) *Interfering subject matter.* An interference exists if the subject matter of a claim of one party would, if prior art, have anticipated or rendered obvious the subject matter of a claim of the opposing party and vice versa.

The Smith Patent is based on an application which is a continuation of application Ser. No. 07/898,019, filed June 12, 1992, now abandoned, which is a continuation of application Ser. No. 07/660,160, filed February 21, 1991, now abandoned, which is a continuation of application Ser. No. 07/106,232, filed October 7, 1987, now abandoned, which is a continuation-in-part of application Ser. No. 06/722,742, filed April 11, 1985, now abandoned, and a continuation-in-part of application Ser. No. 06/689,013, filed January 2, 1985, now abandoned, said application Ser. No. 06/722,742 being a continuation-in-part of application Ser. No. 06/689,013, filed January 2, 1985, now abandoned, which is a continuation-in-part of application Ser. No. 06/570,973, filed January 16, 1984, now abandoned.

Accordingly, the Smith Patent's earliest possible effective filing date is January 16, 1984, one year and four months after Applicants' effective priority date. Applicants therefore submit that they will prevail on priority.

5. Claim Chart Showing Written Description for Each Claim in Applicant's Specification

In accordance with 37 C.F.R. § 41.202(a)(5), attached Appendix D sets forth the written description support for each of Applicants' claims that have been added or amended to provoke the instant interference.

6. Chart Showing Support for a Constructive Reduction to Practice Within the Scope of the Interfering Subject Matter

In accordance with 37 C.F.R. § 41.202(a)(6), attached Appendix E sets forth exemplary disclosure showing "constructive reduction to practice" within the meaning of § 41.201[15] of a representative Engelhardt claim within the scope of the interfering subject matter corresponding to Count 1.

---

[15] 37 C.F.R. § 41.201 provides:

Constructive reduction to practice means a described and enabled anticipation under 35 U.S.C. 102(g)(1) in a patent application of the subject matter of a count. *Earliest constructive reduction to practice* means the first constructive reduction to practice that has been continuously disclosed through a chain of patent applications including in the involved application or patent.

Similarly, attached Appendix F sets forth exemplary disclosure showing constructive reduction to practice of a representative Engelhardt claim within the scope of the interfering subject matter corresponding to Count 2.

CONCLUSION

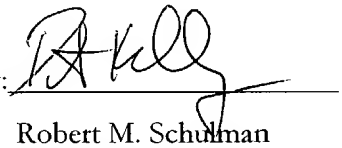
Applicants respectfully request declaration of an interference employing proposed Count 1 and Count 2 set forth in Appendix A:

between Engelhardt Claims 638, 642, 660, 661, 670, 707, 711, 712, 714, 790, 794, 812, 813, 822, 859, 863, 864, 866, 871, 942, 946, 964, 965, 974, 1011, 1015, 1016, 1018, 1023, 1094, 1098, 1116, 1117, 1126, 1163, 1167, 1168, 1170, 1175, 1249, 1267-1270, 1272, 1278, 1288, 1289, 1291, 1297, 1739, 1767, 1768, 1782, 1783 and 1795, and Smith Claims 1-7, 9-16, 19, 23-27 and 54-56, all of which correspond to proposed Count 1; and

between Engelhardt Claims 1769-1773, 1775 and 1796, and Smith Claims 8, 17, 18, 20-22 and 28-53, all of which correspond to proposed Count 2.

Respectfully Submitted
HUNTON & WILLIAMS

Date: Sept. 28, 2004

By: 

Robert M. Schulman
Registration No. 31, 196
David A. Kelly
Registration No. 53,106